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Experimental and Theoretical Studies on the Nucleofugality Patterns in the Aminolysis and Phenolysis of *S*-Aryl *O*-Aryl Thiocarbonates

Enrique A. Castro,*[,†] Margarita Aliaga,[†] Paola R. Campodónico,[‡] Marjorie Cepeda,[†] Renato Contreras,[§] and José G. Santos*[,†]

[†]*Facultad de Química, Pontificia Universidad Católica de Chile, Casilla 306, Santiago 6094411, Chile,* [‡]*Instituto de Ciencias, Facultad de Medicina, Clínica Alemana Universidad del Desarrollo, Santiago 7710162, Chile, and* [§]*Departamento de Química, Facultad de Ciencias, Universidad de Chile, Casilla 653, Santiago, Chile*

jgsantos@uc.cl

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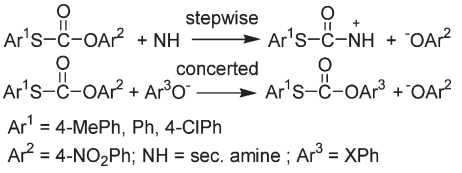

The reactions of *S*-phenyl, *S*-(4-chlorophenyl), and *S*-(2,3,4,5,6-pentafluorophenyl) 4-nitrophenyl thiocarbonates (**9**, **11**, and **16**, respectively) with a series of secondary alicyclic (SA) amines and those of *S*-(4-methylphenyl) 4-nitrophenyl thiocarbonate (**8**) and compounds **9** and **11** with a series of phenols are subjected to a kinetic investigation in 44 wt % ethanol−water, at 25.0 °C and an ionic strength of 0.2 M. The reactions were followed spectrophotometrically. Under nucleophile excess, pseudo-first-order rate coefficients (k_{obsd}) were found. For all these reactions, plots of k_{obsd} vs. free amine or phenoxide anion concentration at constant pH are linear, the slope (k_N) being independent of pH. The Brønsted-type plots (log k_N vs. pK_a of the conjugate acids of the nucleophiles) for the aminolysis of **9**, **11**, and **16** are linear with slopes $\beta = 0.85$, 0.90, and 0.67, respectively. The two former slopes are consistent with a stepwise mechanism, through a zwitterionic tetrahedral intermediate, which breaking to products is rate determining. The latter β value is consistent with a concerted mechanism. The Brønsted-type plots for the phenolysis of thiocarbonates **8**, **9**, and **11** are linear with slopes $\beta = 0.62$, 0.70, and 0.69, respectively. These β values and the absence of curvature at p$K_a = 7.5$ confirm a concerted mechanism. In all these reactions, except those of **16**, the main nucleofuge is 4-nitrophenoxide, being the thio benzenethiolate the minor nucleofuge. For the reactions of thiocarbonate **16** the main nucleofuge is pentafluorobenzenethiolate whereas little 4-nitrophenoxide was found. The reactions of two SA amines with *S*-(3-chlorophenyl) 4-nitrophenyl thiocarbonate (**10**) were subjected to product analysis, showing 60% 4-nitrophenoxide and 40% 3-chlorobenzenethiolate. The study is completed with a theoretical analysis based on the group electrophilicity index, a reactivity descriptor that may be taken as a measure of the ability of a group or fragment to depart from a molecule with the bonding electron pair. The theoretical analysis is in accordance with the experimental results obtained and predicts relative nucleofugalities of *O*-aryl vs. S-aryl groups in a series of diaryl thiocarbonates not experimentally evaluated to date.

Introduction

The kinetics and mechanism of the reactions of several series of nucleophiles with *O*-ethyl *S*-aryl dithiocarbonates is well documented.[1] These reports concern the reactions of these compounds with pyridines, secondary alicyclic (SA) amines, anilines, quinuclidines, phenoxides, and benzenethiolates.[1] On the basis of the Brønsted-type plots

*To whom correspondence should be addressed. Fax: 56-2-6864744. Phone: 56-2-6864742.

(1) (a) Castro, E. A. *Chem. Rev.* **1999**, *99*, 3505. (b) Castro, E. A. *J. Sulfur Chem.* **2007**, *28*, 401.

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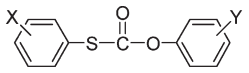
SCHEME 1. Structure of the Thiocarbonates Studied in This Work



Nº	X	Y	Nº	X	Y
1	H	H	**11**	4-Cl	4-NO_2
2	4-CH_3	2,6-diF	**12**	2,4-diF	4-NO_2
3	2,4-diF	2,6-diF	**13**	4-NO_2	H
4	4-Cl	4-Cl	**14**	4-NO_2	4-Cl
5	3-Cl	2,6-diF	**15**	4-NO_2	2,6-diF
6	4-Cl	2,6-diF	**16**	2,3,4,5,6-pentaF	4-NO_2
7	2,3,4,5,6-pentaF	2,6-diF	**17**	4-NO_2	4-NO_2
8	4-CH_3	4-NO_2	**18**	4-NO_2	2,4-diNO_2
9	H	4-NO_2	**19**	2,4-di-NO_2	4-NO_2
10	3-Cl	4-NO_2			

obtained, some of these reactions have been described as stepwise, through a tetrahedral intermediate,[1] and others have been found to be concerted, i.e., with no intermediate, in a single step.[1] In all these reactions the nucleofuge is the less basic benzenethiolate group.

On the other hand, only a few works have appeared on the kinetics of the nucleophilic reactions of *O*-aryl *S*-aryl thiocarbonates.[2] Among these are the following: the aminolysis (SA amines and pyridines) of *O*-phenyl *S*-(4-nitrophenyl) thiocarbonate and *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonate.[2] For the above reactions, where there are two possible nucleofuges and of different nature (benzenethiolates vs. phenoxides), the question is which of the groups is the nucleofuge. In these cases the *S*-aryl groups are less basic than the *O*-aryl groups and the former were always the nucleofuges.

With the aim to assess the nucleofugality of *O*-aryl and *S*-aryl groups, in the present work we undertake a theoretical analysis on thiocarbonates **1**−**19** (structures shown in Scheme 1), as well as a kinetic investigation on the aminolysis (SA amines) of *S*-aryl *O*-(4-nitrophenyl) thiocarbonates (aryl = phenyl, 4-chlorophenyl, and 2,3,4,5,6-pentafluorophenyl: **9**, **11**, and **16**, respectively) and the phenolysis of *S*-(4-methylphenyl) *O*-(4-nitrophenyl) thiocarbonate (**8**) and thiocarbonates **9** and **11**. Also, a HPLC analysis of the reaction products is carried out to evaluate the nucleofugality of the leaving groups involved in the above thiocarbonates and in the reactions of *S*-(3-chlorophenyl) 4-nitrophenyl thiocarbonate (**10**) with piperidine and morpholine. The experimental investigation is complemented with the theoretical analysis, which makes use of the nucleofugality index recently introduced by Contreras et al.[3] We report the nucleofugality values of the fragments *S*-aryl and *O*-aryl for the series of *S*-aryl *O*-aryl thiocarbonates **1**−**19**.

Results and Discussion

The pseudo-first-order rate constants (k_{obsd}), obtained under nucleophile (SA amine or phenoxide) excess, for all the reactions obey eq 1, where k_0 and k_N are the rate coefficients for solvolysis and aminolysis or phenolysis of the substrates, respectively. The values of k_0 and k_N show no dependence on pH within the pH range employed. These values were obtained as the intercept and slope, respectively, of linear plots of k_{obsd} against free nucleophile concentration, at constant pH.

$$k_{obsd} = k_0 + k_N[\text{free nucleophile}] \quad (1)$$

For the studied reactions, the k_0 values were much smaller than the k_N [free nucleophile] term in eq 1. The values of k_N for the reactions of thiocarbonates **9**, **11**, and **16** with SA amines and those of compounds **8**, **9**, and **11** with phenoxides are shown in Tables 1 and 2, respectively.

Figures 1 and 2 show the Brønsted-type plots for the aminolysis and phenolysis studied, respectively. The k_N values for the SA aminolysis, as well as those of the pK_a of the conjugate acids of the SA amines, were statistically corrected with $q = 2$ for piperazine ($q = 1$ for all the other SA amines) and $p = 2$ for all the conjugate acids of the amines, except that for piperazinium ion with $p = 4$.[4] The parameter q is the number of equivalent basic sites on the free amine and p is the number of equivalent dissociable protons on the conjugate acid of the amine.[5]

The values found of the Brønsted slopes (β) are 0.86, 0.89, and 0.67 for the aminolysis of thiocarbonates **9**, **11**, and **16**, respectively, and 0.62, 0.70, and 0.69 for the phenolysis of **8**, **9**, and **11**, respectively. The values of the Brønsted slopes for the aminolysis of **9** and **11** (0.86, 0.89) are in accordance with the β values found for stepwise reactions, through a zwitterionic tetrahedral intermediate ($T^{\pm}$), where departure of the nucleofuge from $T^{\pm}$ to give the final products is the rate-determining step ($\beta = 0.8-1.1$). This is

(2) Castro, E. A.; Aliaga, M.; Santos, J. G. *J. Phys. Org. Chem.* **2008**, *21*, 271.
(3) Campodónico, P. R.; Aizman, A.; Contreras, R. *Chem. Phys. Lett.* **2006**, *422*, 340.
(4) Castro, E. A.; Ureta, C. *J. Chem. Soc., Perkin Trans. 2* **1991**, 63.
(5) Bell, R. P. *The Proton in Chemistry*; Methuen: London, UK, 1959; p 159.

TABLE 1. Values of pK_a for the Conjugate Acids of Secondary Alicyclic (SA) Amines and k_N Values for the Reactions of SA Amines with *S*-Phenyl 4-Nitrophenyl Thiocarbonate (9), *S*-(4-Chlorophenyl) 4-Nitrophenyl Thiocarbonate (11), and *S*-(Pentafluorophenyl) 4-Nitrophenyl Thiocarbonate (16)[a]

		$k_N/s^{-1}\ M^{-1}$		
SA amine	pK_a	**9**	**11**	**16**
piperidine	10.82	3.6 ± 0.2	8.3 ± 0.3	1680 ± 60
piperazine	9.71	0.42 ± 0.01	0.76 ± 0.05	340 ± 30
1-(2-hydroxyethyl)piperazine	9.09	0.150 ± 0.005	0.25 ± 0.01	103 ± 4
morpholine	8.48	0.063 ± 0.003	0.081 ± 0.002	60 ± 3
1-formylpiperazine	7.63	0.0059 ± 0.0002	0.0092 ± 0.0006	8.5 ± 0.3
piperazinium ion	5.37			0.25 ± 0.05

[a]Both the pK_a and k_N values were determined in 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl).

TABLE 2. Values of pK_a for the Phenols and k_N Values for the Phenolysis of *S*-(4-methylphenyl) 4-Nitrophenyl Thiocarbonate (8), *S*-Phenyl 4-Nitrophenyl Thiocarbonate (9), and *S*-(4-Chlorophenyl) 4-Nitrophenyl Thiocarbonate (11)[a]

		$k_N/s^{-1}\ M^{-1}$		
phenoxide substituent	pK_a	**8**	**9**	**11**
4-OCH_3	11.55	1.38 ± 0.04	1.14 ± 0.05	5.9 ± 0.1
H	11.16	0.27 ± 0.01	0.38 ± 0.01	1.40 ± 0.06
3-Cl	10.23	0.14 ± 0.01	0.27 ± 0.01	0.77 ± 0.03
3-CN	9.23	0.065 ± 0.002		
4-CN	8.42	0.0102 ± 0.0003	0.0191 ± 0.0009	0.043 ± 0.001
2,6-F_2	8.21	0.0044 ± 0.0002	0.0053 ± 0.0003	0.021 ± 0.001
2,4,6-F_3	7.95	0.0062 ± 0.0001		
2,3,4,5,6-F_5	5.45		0.00005 ± 0.00001	0.00025 ± 0.00005

[a]Both the pK_a and k_N values were determined in 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 mol·dm^{-3} (KCl).

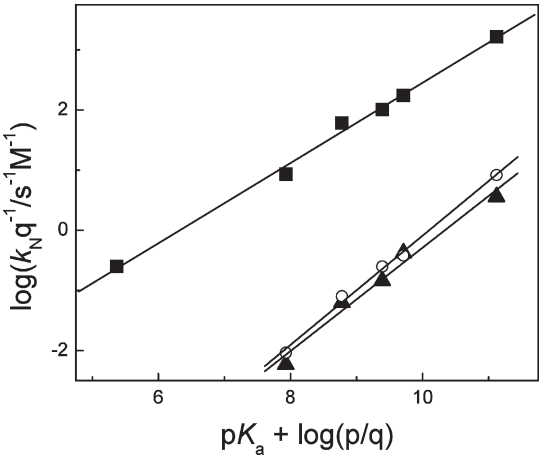


FIGURE 1. Brønsted-type plots (statistically corrected, see text) for the reactions of SA amines with (▲) *S*-phenyl 4-nitrophenyl thiocarbonate (**9**), (○) *S*-(4-chlorophenyl) 4-nitrophenyl thiocarbonate (**11**), and (■) *S*-(pentafluorophenyl) 4-nitrophenyl thiocarbonate (**16**) in 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl).

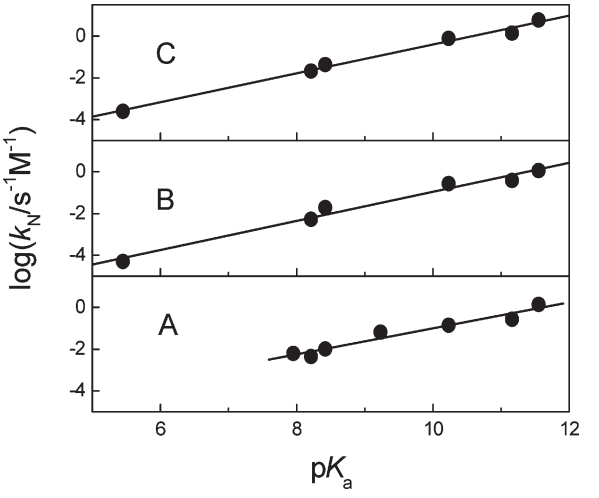
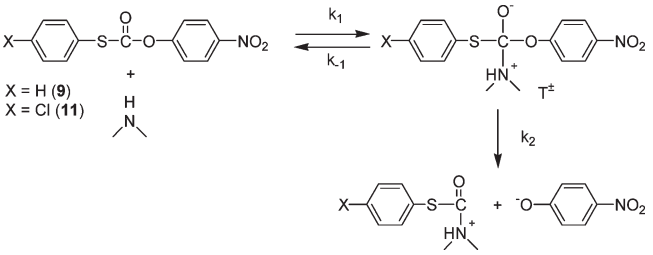


FIGURE 2. Brønsted-type plots for the phenolysis of (A) *S*-(4-methylphenyl) 4-nitrophenyl thiocarbonate (**8**), (B) *S*-phenyl 4-nitrophenyl thiocarbonate (**9**) and (C) *S*-(4-chlorophenyl) 4-nitrophenyl thiocarbonate (**11**), in 44 wt % ethanol−water, at 25.0 °C, ionic strength 0.2 M (KCl).

the case of the aminolysis of diaryl carbonates,[1b,6,7] aryl benzoates and thiolbenzoates,[8] aryl thionocarbamates,[9] and *O*-alkyl *S*-aryl and *O*-aryl *S*-aryl thiocarbonates.[1,2]

Taking into account the β values found for the SA aminolysis of thiocarbonates **9** and **11** and the product

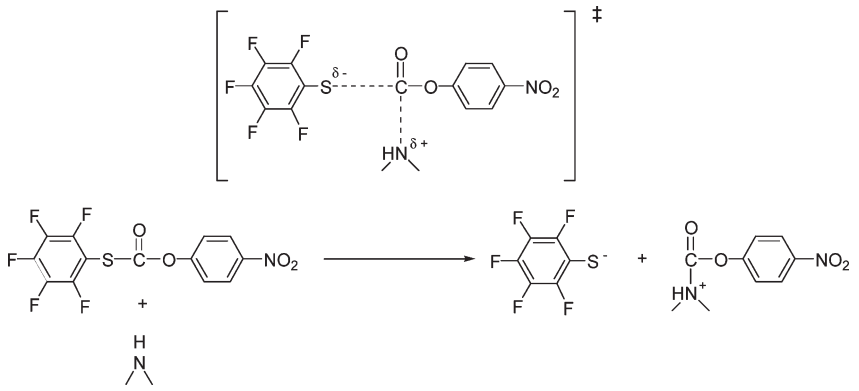
SCHEME 2



analysis (4-nitrophenoxide is the main leaving group) the most probable mechanism is that described in Scheme 2,

(6) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963.
(7) Um, I.-H.; Yoon, S.; Park, H.-R.; Han, H.-J. *Org. Biomol. Chem.* **2008**, *6*, 1618. Um, I.-H.; Kim, E. Y.; Park, H.-R.; Jeon, S.-E. *J. Org. Chem.* **2006**, *71*, 2302.
(8) Seo, J.-A.; Lee, H.-M.; Um, I.-H. *Bull. Korean Chem. Soc.* **2008**, *29*, 1915. Seo, J.-A.; Chun, S.-M.; Um, I.-H. *Bull. Korean Chem. Soc.* **2008**, *29*, 1459. Ahn, J.-A.; Park, Y.-M.; Um, I.-H. *Bull. Korean Chem. Soc.* **2009**, *30*, 214.
(9) Park, S. Y.; Oh, H. K. *Bull. Korean Chem. Soc.* **2009**, *30*, 749.

SCHEME 3



where the expulsion of 4-nitrophenoxide from the intermediate $T^{\pm}$ is the rate-determining step.

Tables 1 and 2 and Figures 1 and 2 show that thiocarbonate **11** is about 1.3 to 5 times more reactive than **9**. This is attributed to the greater electron withdrawing ability of 4-chlorobenzenethiolate than benzenethiolate leading to a more positive carbonyl carbon atom and, therefore, more prone to the nucleophilic attack.

The mechanism of the reactions of 4-methylphenyl and 4-chlorophenyl 4-nitrophenyl carbonates with SA amines in 44 wt % ethanol−water is stepwise, as shown by the biphasic Brønsted plots obtained with a curvature center (pK_a^0) at pK_a = 10.5 and 10.6, respectively.[10a,b] Since the same aminolysis of thiocarbonates **9** and **11** in the same solvent shows linear Brønsted plots up to pK_a 10.8 (this work), it means that $pK_a^0 > 10.8$ for these reactions. Namely, the change of 4-methylphenoxy by benzenethio or 4-chlorophenoxy by 4-chlorobenzenethio as nonleaving groups in the substrates increases the pK_a^0 value. Since for both types of reactions expulsion of the 4-nitrophenoxide ion is the rate-determining step, the pK_a^0 augment can be explained by a greater electron-withdrawing ability of the thio nonleaving groups, compared to their oxy counterparts, as judged by their basicities (for instance, the pK_a of 4-chlorobenzenethiol and 4-chlorophenol in water are 6.0 and 9.4, respectively). This is in agreement with the results obtained by Gresser and Jencks in the aminolysis of diaryl carbonates: the stronger the electron withdrawal from the nonleaving group the larger the pK_a value at the center of the Brønsted curvature.[11] In the same line, the reactions of 4-nitrophenyl methyl carbonate with SA amines show $pK_a^0 = 9.3$,[12] compared to $pK_a^0 > 10.8$ for the SA aminolysis of thiocarbonates **9** and **11**. Namely, the change of methoxy by either benzenethio or 4-chlorobenzenethio as a nonleaving group results in a larger pK_a^0 value. The change of MeO by MeS as a nonleaving group also enlarges the pK_a^0 value, as shown by $pK_a^0 = 9.3$ found for the SA aminolysis of 4-nitrophenyl methyl carbonate,[12] in comparison with the linear Brønsted plot up to pK_a 11.2 (i.e, $pK_a^0 > 11.2$) obtained for the same aminolysis of 4-nitrophenyl *S*-methyl thiocarbonate.[13]

It is noteworthy that in the above reactions of thiocarbonates **9** and **11** the main leaving group is 4-nitrophenoxide, despite that the benzenethiolate groups involved are less basic (pK_a values of 4-nitrophenol, benzenethiol, and 4-chlorobenzenethiol are 7.5, 6.4, and 6.0, respectively, in 44 wt % ethanol−water). Although it is known that phenoxide groups are better nucleofuges than *isobasic* benzenethiolates,[14] it is surprising that 4-nitrophenoxide is the main leaving group in the aminolysis of **11** despite being 1.5 pK_a units more basic than 4-chlorobenzenethiolate. Nevertheless, when 4-nitrophenoxide is compared with 3-chlorobenzenethiolate (pK_a 5.5 of conjugate acid) as leaving groups, as in the SA aminolysis of thiocarbonate **10**, the ratio of nucleofugalities is 4-nitrophenoxide/3-chlorobenzenethiolate = 1.5 (see the Product Studies section).

On the other hand, the β value found for the SA aminolysis of thiocarbonate **16** (β = 0.67) is in accordance with those obtained in the concerted aminolysis of *O*-alkyl and *O*-aryl *S*-aryl thiocarbonates,[1,2,15] *O*-ethyl *S*-aryl dithiocarbonates,[16] and alkyl aryl and diaryl carbonates.[1b] This suggests that the aminolysis of **16** is ruled by a concerted mechanism. Taking also into account that pentafluorobenzenethiolate is the main leaving group of the substrate (see the Product Studies section), the most probable mechanism for this reaction is that shown in Scheme 3.

It is known that the β value alone is not enough to conclude that a mechanism is concerted. It is also necessary to make sure that the expected pK_a value at the center of the Brønsted curvature (pK_a^0) for a hypothetical stepwise mechanism is within the pK_a range used.[17,18]

As the Brønsted plot for the aminolysis of **16** in Figure 1 does not show a break, there are two possibilities: (i) If the mechanism is stepwise and the curvature center is located at a pK_a value greater than 11, the experimental β value (0.67) should correspond to β_2 (the Brønsted slope when breakdown to products of the tetrahedral intermediate is rate determining).[1] Nevertheless, this value is too small to be

(10) (a) Castro, E. A.; Andujar, M.; Campodónico, P.; Santos, J. G. *Int. J. Chem. Kinet.* **2002**, *34*, 309. (b) Castro, E. A.; Andujar, M.; Toro, A.; Santos, J. G. *J. Org. Chem.* **2003**, *68*, 3608.

(11) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6970.

(12) Castro, E. A.; Aliaga, M.; Campodónico, P.; Santos, J. G. *J. Org. Chem.* **2002**, *67*, 8911.

(13) Castro, E. A.; Aliaga, M.; Santos, J. G. *J. Org. Chem.* **2005**, *70*, 2679.

(14) (a) Douglas, K. T.; Alborz, M. *J. Chem. Soc., Chem. Commun.* **1981**, 551. (b) Douglas, K. T. *Acc. Chem. Res.* **1986**, *19*, 186.

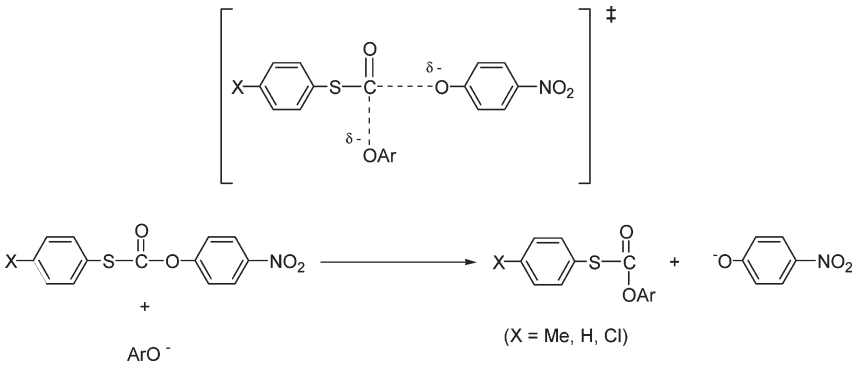
(15) Oh, H. K.; Lee, Y. H.; Lee, I. *Int. J. Chem. Kinet.* **2000**, *32*, 131.

(16) Oh, H. K.; Lee, J. Y.; Yun, J. H.; Park, Y. S.; Lee, I. *Int. J. Chem. Kinet.* **1998**, *30*, 419. Oh, H. K.; Oh, J. Y.; Sung, D. D.; Lee, I. *Collect. Czech. Chem. Commun.* **2004**, *69*, 2174.

(17) (a) Chrystiuk, E.; Williams, A. *J. Am. Chem. Soc.* **1987**, *109*, 3040. (b) Williams, A. *Acc. Chem. Res.* **1989**, *22*, 387.

(18) Williams, A. *Free Energy Relationships in Organic and Bio-Organic Chemistry*; The Royal Society of Chemistry: Cambridge, UK, 2003; p 171.

SCHEME 4



considered as β_2 since these values are usually 0.8−1.1.[1] (ii) If the Brønsted curvature were centered at a pK_a smaller than 6, the rate-limiting step would be formation of the tetrahedral intermediate; in these cases the slope (β_1) value is usually 0.1−0.3.[1] The β value found (0.67) looks too large to be considered as corresponding to β_1. Therefore, the stepwise mechanism is unlikely for the aminolysis of **16**.

Furthermore, the reactions of SA amines with *O*-phenyl and *O*-(4-chlorophenyl) *S*-(4-nitrophenyl) thiocarbonates in aqueous ethanol have been described by a concerted mechanism.[2] Therefore, for these reactions the putative tetrahedral intermediate does not exist or it is highly unstable. If simultaneously the leaving group 4-nitrobenzenethiolate is changed by pentafluorobenzenethiolate, a better nucleofuge, and the nonleaving phenoxy or 4-chlorophenoxy groups are changed by the more electron withdrawing 4-nitrophenoxy group, obviously the putative tetrahedral intermediate would be even more unstable and it is, therefore, reasonable that the mechanism for the aminolysis of **16** be concerted.

For the phenolysis reactions of thiolcarbonates **8**, **9**, and **11** the values of the Brønsted slopes found (0.62, 0.70, and 0.69, respectively) are in accordance with those obtained in the concerted phenolysis reactions of alkyl *S*-aryl thiocarbonates[1b] and alkyl aryl and diaryl carbonates.[1b] They are also in agreement with the concerted phenolysis of the following esters: 4-chloro 2-nitrohenyl acetate ($\beta = 0.64$),[19] 2,4-dinitrophenyl acetate ($\beta = 0.59$),[20] 3-nitrophenyl, 4-nitrophenyl, and 3,4-dinitrophenyl formates ($\beta = 0.64$, 0.51, and 0.43, respectively)[21] and the corresponding acetates ($\beta = 0.66$, 0.59, and 0.53, respectively).[21] They are also in line with the slopes found in the concerted phenolysis of phthalic and maleic anhidrides ($\beta =$ 0.45 and 0.56, respectively).[22] Therefore, the β values obtained in the phenolysis of thiocarbonates **8**, **9**, and **11** suggest that these reactions are ruled by a concerted mechanism.

As mentioned above, the magnitude of β is not sufficient to validate the concerted mechanism.[17,18] For the following two reasons we are more inclined toward the concerted mechanism for the phenolysis of thiolcarbonates **8**, **9**, and **11**: (i) The phenolysis reactions of aryl 4-nitrophenyl carbonates (aryl = 4-chlorophenyl and 4-methylphenyl) are concerted; therefore, the putative tetrahedral intermediates do not exist or are highly unstable.[23] The change of the *O*-aryl groups by the corresponding *S*-aryl groups should result in even less stable tetrahedral intermediates, in view of the greater electron withdrawal from the latter groups, confirming, therefore, the concerted mechanism for the phenolysis of **8**, **9**, and **11**; (ii) if the mechanism were stepwise for the phenolysis of thiocarbonates **8**, **9**, and **11**, where 4-nitrophenoxide anion is the main leaving group, the expected value of the center of the Brønsted curvature (pK_a^0) would be at 7.5 (the pK_a value of 4-nitrophenol in 44 wt % ethanol−water) due to the fact that the nucleophile (a phenoxide anion) and the nucleofuge (4-nitrophenoxide) are of the same nature. The absence of a Brønsted curvature at pK_a 7.5 in Figure 2 allows the concerted mechanism to be confirmed. This is shown in Scheme 4.

In the concerted phenolysis of thiocarbonates **8**, **9**, and **11** the 4-nitrophenoxide group is the main nucleofuge even though the corresponding benzenethiolates are less basic. This result suggests that the transition state to expel the 4-nitrophenoxide group is less energetic, relative to reactants, than that to expel the benzenethiolate group.

From these results it is possible to conclude that 4-nitrophenoxide is the main leaving group (96(±4)%) even when the *S*-aryl group is 1.2 pK_a units (in water) more basic, as in thiocarbonate **11** (see Table 3). When the difference in pK_a is much greater, as in thiocarbonate **16** (pK_a of 4-nitrophenol and 2,3,4,5,6-pentafluorobenzenethiol in water are 7.2 and 2.7, respectively), the *S*-aryl group is the main nucleofuge (96(±4)%). When the difference in pK_a is greater than 1.2 (in water) but smaller than ca. 4, as in thiocarbonate **10** (ΔpK_a 1.7, see Table 3), the ratio of nucleofugalities 4-nitrophenoxide/*S*-3-chlorobenzenethiolate is about 1.5, as shown by the UV−vis and HPLC analyses carried out at the end of the reactions of **10** with two SA amines: piperidine and morpholine (see the Product Studies section). To explain these results, we undertook the following computational study.

Computational Study. To verify the experimental patterns of nucleofugality observed, both in the aminolysis and phenolysis of thiocarbonates, the nucleofugality index was calculated for a series of fragments involved as leaving groups in thiocarbonates **1**−**19**.[3] The results of the calculations are summarized in Table 3 (atom coordinated and absolute energies of calculated structures for thiocarbonates **1**−**19** are shown in Table S7 in the Supporting Information) for a series of fragments: X-substituted benzenethio (ω_S) and Y-substituted phenoxy (ω_O) groups.

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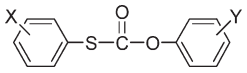
TABLE 3. Global Electrophilicity Index (ω), Nucleofugality Values for the X-Substituted Benzenethio (ω_S) and Y-Substituted Phenoxy (ω_O) Fragments for Thiocarbonates 1−19, Evaluated at the HF/6-311G (d,p) Level of Theory, and Experimental pK_a Values for Each Fragment[a]



						main nucleofuge	
no.	ω (eV)	pK_a	ω_S (eV)	pK_a	ω_O (eV)	exptl	predicted
1	0.42	6.4	0.39	9.9	0.02		X-PhS
2	0.41	6.5	0.29	7.1	0.11		X-PhS
3	0.50	5.0	0.43	7.1	0.06		X-PhS
4	0.51	6.0	0.42	9.4	0.02		X-PhS
5	0.51	5.5	0.46	7.1	0.03		X-PhS
6	0.52	6.0	0.46	7.1	0.04		X-PhS
7	0.66	2.7	0.58	7.1	0.02		X-PhS
8	0.72	6.5	0.01	7.2	0.71	Y-PhO	Y-PhO
9	0.76	6.4	0.01	7.2	0.74	Y-PhO	Y-PhO
10	0.78	5.5	0.01	7.2	0.76	Y-PhO[b]	Y-PhO
11	0.79	6.0	0.01	7.2	0.77	Y-PhO	Y-PhO
12	0.80	5.0	0.01	7.2	0.79		Y-PhO
13	0.83	4.6	0.65	9.9	0.00	X-PhS	X-PhS
14	0.86	4.6	0.67	9.4	0.01	X-PhS	X-PhS
15	0.89	4.6	0.83	7.1	0.00		X-PhS
16	0.91	2.7	0.86	7.2	0.03	X-PhS	X-PhS
17	1.01	4.6	0.78	7.2	0.03		X-PhS
18	1.15	4.6	0.04	4.1	1.10		Y-PhO
19	1.21	3.4	1.18	7.2	0.00		X-PhS

[a]The pK_a values shown are in water, at 25.0 °C. [b]60% Y-PhO and 40% X-PhS, as found by products analysis.

The study includes those compounds evaluated herein, others assessed previously, and some compounds not experimentally studied. It may be seen that the nucleofugality shows an inverse variation pattern with the pK_a of the molecule. This result may highlight the role of the electron-withdrawing and electron-releasing substituent on the nucleofugality of the leaving group.[3,24] For instance, for thiocarbonates **1**−**7** and **17** the leaving group ability appears almost concentrated on the fragment X-PhS. This result may be traced to the presence of the soft S atom in this subunit that may confer to it an enhanced polarizability, a factor on which the nucleofugality pattern depends. This result is also consistent with an enhanced ability of the fragment to better stabilize the negative charge upon departing from the structure at the final stage of the process. Note that for compounds **8** −**15**, **18**, and **19** the presence of the strong electron-withdrawing $-NO_2$ group always results in an enhanced nucleofugality pattern. This effect is being probed here at the strongly favorable para-position.

On the other hand, for those compounds kinetically evaluated, such as **9** (this paper) and **13**,[2] it may be seen in Table 3 that exchange of the position pattern of the $-NO_2$ group results in an enhancement in nucleofugality at the end where this group is located. Note further that for a similar exchange involving this time the −Cl atom in compounds **11** (this paper) and **14**,[2] a similar pattern is observed. A final useful test may be obtained by comparing compounds **16** (experimentally studied in this work) and compounds **12** and **15** (predicted). For compound **16**, pentafluoro substitution, together with the presence of the soft S atom, cooperatively contributes to a significant electrophilic activation that leads to the departure of the fragment X-PhS. However, for compounds **12** and **15** the prediction is in agreement with the empirical rule stating that the fragment bearing the $-NO_2$ group will always be the leaving group, thereby suggesting that disubstitution at the ortho−para and ortho−ortho positions at any ring is not as efficient as the $-NO_2$ group alone in the para-position. This result deserves experimental verification. In summary, the leaving group ability, as defined by the group electrophilicity in eq 4 (see the Experimental Section), seems to be a simple and useful tool to describe nucleofugality patterns in polyfunctional structures bearing different patterns of chemical substitution.

Comparison of thiocarbonates **2** with **8**, **5** with **10**, and **6** with **11**, where the same *S*-aryl group is present, shows that if there is a *O*-NO_2 group (pK_a = 7.5 in 44 wt % ethanol−water) the latter leaves, but if there is a *O*-difluoro group (pK_a = 7.8 in 44 wt % ethanol−water) the benzenethiolate group leaves, despite both *O*-aryl groups showing very similar pK_a values.

During the review process a referee asked for more evidence to validate the nucleofugality index. The products study of compound **10** with HPLC data shows, as we quote in Table 3, two products corresponding to the detachment of the fragments 4-nitrophenol (60% yield) and 3-chlorobenezenethiol (40%). Despite the fact that the theoretical nucleofugality index predicts the detachment of the fragment corresponding to 4-nitrophenol, the product that is in major proportion, this index cannot account for the formation of a second nucleofuge when there is a significant competition between the two nucleofuges. This is a limitation of the model for those cases bearing two competitive nucleofuges and must be considered when the theoretical index is used at the ground state of reactants.

Experimental Section

Materials. Thiocarbonates **8**, **9**, **10**, **11**, and **16** were synthesized by the reaction of 4-nitrophenyl chloroformate with the corresponding benzenethiolate, in diethyl ether, under nitrogen, in the presence of pyridine.[2,6] The reaction mixture was washed with cold acid water and dried with $MgSO_4$. The products were purified in a silica column with chloroform−hexane as eluant. The products were characterized by the following properties:

***S*-4-Methylphenyl 4-nitrophenyl thiocarbonate (8):** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26 (d, 2H, J = 8.1 Hz), 7.38 (d, 2H, J = 9.2 Hz), 7.48 (d, 2H, J = 8.1 Hz), 8.26 (d, 2H, J = 9.2 Hz), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.7, 155.8, 145.5, 140.9, 134.9, 130.4, 125.3, 122.7, 122.0, 21.5. HRMS calcd for $C_{14}H_{11}NO_4S$ 289.04088, found 289.04013.

***S*-Phenyl 4-nitrophenyl thiocarbonate (9):** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (d, 2H), 7.46 (t, 3H, J = 9.1 Hz), 7.61 (d, 2H), 8.28 (d, 2H, J = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.3, 155.7, 145.5, 134.9, 130.3, 129.6, 126.4, 125.3, 121.9. HRMS calcd for $C_{13}H_9NO_4S$ 275.02623, found 275.02495.

***S*-3-Chlorophenyl 4-nitrophenyl thiocarbonate (10):** ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 7.35−7.53 (m, 5H), 7.62 (s, 1H), 8.28 (d, 2H, J = 9.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 167.5, 155.5, 145.6, 135.1, 134.6, 132.9, 130.6, 130.5, 127.9, 125.4, 122.0. HRMS calcd for $C_{13}H_8ClNO_4S$ 308.98626, found 308.98623.

***S*-4-Chlorophenyl 4-nitrophenyl thiocarbonate (11):** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40 (d, 2H), 7.41 (d, 1H), 7.50 (d, 1H, J = 9.2 Hz), 8.29 (d, 1H), 8.30 (d, 2H), 8.35 (d, 1H, J = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 163.7, 155.2, 145.9, 126.2, 125.6, 125.5, 121.8, 121.7, 115.7. HRMS calcd for $C_{13}H_8ClNO_4S$ 308.98626, found 308.98565.

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***S*-2,3,4,5,6-Pentafluorophenyl 4-nitrophenyl thiocarbonate (16):** ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.50 (d, 2H, J = 9.1 Hz), 8.35 (d, 2H, J = 9.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 155.1, 152.4, 150.3, 146.2, 144.9, 141.1, 136.5, 132.9, 125.8, 121.9, 119.4; ^{19}F NMR (200 MHz, $CDCl_3$) δ (ppm) −128.3 (F_{orto}), −140.3 (F_{para}), −162.7 (F_{meta}).

Anal. Calcd for $C_{13}H_4F_5NO_4S$: C, 42.75; H, 1.10; N, 3.84; S, 8.78. Found: C, 42.51; H, 1.23; N, 3.96; S, 8.53.

Kinetic Measurements. The kinetics of the reactions were analyzed through a diode array spectrophotometer in 44 wt % ethanol−water, at 25.0 ± 0.1 °C and an ionic strength of 0.2 M (maintained with KCl). The reactions were followed at the 300−500 nm wavelength range.

The reactions were studied under at least 10-fold excess of total amine (free amine + its conjugate acid) or total phenol (free phenoxide + phenol) over the substrate, the initial concentration of the latter being 2.5×10^{-5} M. Under these conditions pseudo-first-order rate coefficients (k_{obsd}) were found throughout, the kinetics being measured for at least five half-lives at the corresponding wavelengths. These were 400 nm, when following 4-nitrophenoxide ion formation, for the reactions of thiocarbonates **8**, **9**, and **11**, and 310 nm, when following the formation of the corresponding 4-nitrophenyl carbamate for the aminolysis of thiocarbonate **16**. In all the reactions the pH was maintained constant by the buffer formed by partial protonation of the nucleophile or by the addition of an external buffer.

The reactions of thiocarbonate **16** with piperazine and piperazinium ion were studied at pH 7.2−8.1, where mixtures of both amines are present. In these cases the k_N values were obtained through eqs 2 and 3. In these equations k_{Nobsd} is a global nucleophilic rate constant (corresponding to the mixture of nucleophiles), $[N]_{tot}$ is the total piperazine (piperazine + piperazinium ion) concentration, F_N and F_{NH} are the molar fractions of piperazine and piperazinium ion, respectively, and k_N and k_{NH} are their corresponding nucleophilic rate constants. The values of k_{Nobsd} were obtained as the slopes of linear plots of k_{obsd} vs. $[N]_{tot}$ at constant pH. The nucleophilic rate constants for the reactions of thiocarbonate **16** with piperazine (k_N) and piperazinium ion (k_{NH}) were determined through eq 3, as described.[4]

$$k_{obs} = k_0 + k_{Nobs}[N]_{tot} \quad (2)$$

$$k_{Nobs} = F_N k_N + F_{NH} k_{NH} \quad (3)$$

The k_{obsd} values obtained and the experimental conditions for the studied reactions are shown in Tables S1−S6 in the Supporting Information.

Product Studies. For the SA aminolysis of thiocarbonates **9** and **11** and the phenolysis of **8**, **9**, and **11**, 4-nitrophenolate anion (96(±4)%) was identified as one of the products of the reactions, by comparison of both the UV−vis and HPLC spectra, after completion of these reactions, with those of an authentic sample of 4-nitrophenol, under the same reaction conditions. For the reactions of **8**, **9**, and **11**, only traces (not quantified) of the corresponding benzenethiolates were detected by HPLC analysis, being these traces attributed to the formation of these compounds either by the parallel hydrolysis of the substrates or by their nucleophilic reactions.

In the reactions of thiocarbonates **9** and **11** with morpholine, the formation of the corresponding 4-nitrophenyl carbamate was not detected by HPLC analysis (less than 1%), with this compound, therefore, being disregarded (or being insignificant) as one of the reaction products.

For the reactions of thiocarbonate **16** with morpholine, the corresponding 4-nitrophenyl carbamate was identified as one of the products by comparison of its retention time in HPLC with that of an authentic sample, under the same reaction conditions of the kinetics. The HPLC analysis at the end of these reactions showed only traces (less than 1%) of 4-nitrophenol formation, attributed to either the hydrolysis of the *S*-aryl *O*-4-nitrophenyl thiocarbonate product or the direct nucleophilic reaction of the substrate.

For the reactions of thiocarbonate **10** with piperidine (0.1 M, pH 10.8) and morpholine (0.08 M, pH 8.9) in the same experimental conditions as those of the kinetic measurements of the reactions with the other substrates, two analyses were performed at the end of the reactions: (i) The absorbance at 400 nm was compared with that of a sample of 4-nitrophenol at the same conditions, and also with the final absorbance obtained in the reaction of the substrate, at the same concentration as 4-nitrophenol in the previous experiment, with NaOH. (ii) By HPLC analysis, the signal of 4-nitrophenol in the mixture at the end of the reactions was compared (with respect to retention time and UV−vis spectrum) with that corresponding to 4-nitrophenol and quantified in comparison with a calibration curve. Both results show 60% 4-nitrophenol and 40% 3-chlorobenzenethiol in the final mixture.

Computational Study. One of the most relevant achievements of the research work carried out in the field of theoretical physical organic chemistry has been the introduction of reactivity indexes to analyze reactivity, selectivity, and site activation in modern texts of Organic Chemistry.[25] On the basis of these concepts, it has been proposed that the regional electrophilicity of a chemical fragment, given by the global electrophilicity index weighted by the electrophilic Fukui function, can be taken as a measure of the ability of the group to depart from a molecule with the bonding electron pair.[3] The nucleofugality index ν(PG) has been given by the following definition:[3]

$$\nu(PG) \equiv \sum_{k\varepsilon PG} \omega_k \quad (4)$$

where ω_k is the local or the condensed to atom electrophilicity, obtained by multiplying the global electrophilicity w, proposed by Parr et al.,[25,26] by the corresponding electrophilic Fukui finction.[3] The permanent group (PG) dependence on the nucleofugality index is stressed in eq 4. The nucleofugality index will be used to rank the heterolytic group detachment ability in the series of thiocarbonates experimentally studied in this work. Following the experimental results, these substrates may be classified as described in Table 3. Ab initio HF/6-311G (d,p) calculations were performed with the Gaussian 98 suite of programs[27] in order to evaluate the electronic quantities required to calculate the ground state electrophilicity index for the series of thiocarbonates considered in the present study.

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Supporting Information Available: Kinetics conditions and results for the reactions of thiocarbonates **8**, **9**, **11**, **16** (Tables S1−S6), NMR spectra of thiocarbonates **8**, **9**, **10**, **11**, **16**, and atom coordinated and absolute energies of calculated structures for thiocarbonate **1**−**19** (Table S7). This material is available free of charge via the Internet at http://pubs.acs.org.

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